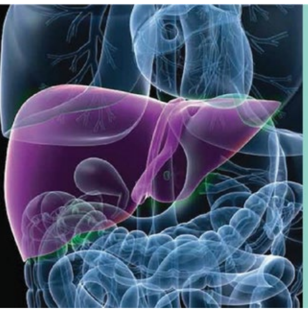

Surveillance and Diagnosis of Hepatocellular Carcinoma

Jane Lim, M.D., M.S., and Amit G. Singal, M.D., M.S.

Hepatocellular carcinoma (HCC) surveillance has been shown to improve early tumor detection, curative treatment receipt, and overall survival.[1] Therefore, several professional societies, including the American Association for the Study of Liver Diseases (AASLD), recommend HCC surveillance every 6 months in at-risk patients, including those with cirrhosis.[2] (Table 1) Although there have been increasing reports of HCC developing in patients with noncirrhotic nonalcoholic fatty liver disease (NAFLD), this population is not currently included in surveillance guideline recommendations. A large cohort study of patients with NAFLD from the Veterans Affairs health system suggests that although 20% of patients with NAFLD do not have cirrhosis at the time of HCC diagnosis, the annual incidence rate is too low for surveillance to be cost-effective.[3] The most recent AASLD guidelines incorporated key changes to HCC surveillance and diagnostic algorithms, including inclusion of alpha-fetoprotein (AFP) for surveillance and assimilation of Liver Imaging Reporting and Data System (LI-RADS) criteria for HCC diagnosis.[2] Herein, we review these updated recommendations for surveillance and diagnosis.

HCC SURVEILLANCE

Ultrasonography, the best studied imaging modality for HCC surveillance, has long been recommended given several advantages, including being readily available, well tolerated, and noninvasive. A meta-analysis of surveillance cohort studies demonstrated ultrasound has an acceptable sensitivity of 84% (95% confidence interval [CI]: 76%-92%) for detecting any-stage HCC; however, its sensitivity for early-stage HCC detection is significantly lower, at only 47% (95% CI: 33%-61%).[4] Further, its effectiveness can be affected by factors such as operator expertise, severity of liver disease, and patient body habitus, leading to wide variation in its sensitivity between centers and patients.[5]

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; CI, confidence interval; CT, computed tomography; DCP, des-γ-carboxyprothrombin; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; OPTN, Organ Procurement and Transplantation Network; RR, relative risk.

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TABLE 1. AT-RISK GROUPS FOR WHOM HCC SURVEILLANCE IS RECOMMENDED

Patients with cirrhosis:

- Hepatitis C cirrhosis
- Hepatitis B cirrhosis
- Alcohol-related cirrhosis
- Nonalcoholic steatohepatitis–related cirrhosis
- Stage 4 primary biliary cholangitis with cirrhosis
- Genetic hemochromatosis with cirrhosis
- alpha-1-antitrypsin deficiency with cirrhosis
- Cirrhosis of other causative factors

Patients with hepatitis B infection but without cirrhosis:

- Asian male hepatitis B carriers ≥40 years old
- Asian female hepatitis B carriers ≥50 years old
- Hepatitis B carriers with family history of HCC
- African/North American black individuals with hepatitis B who are ≥20 years old

Although contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) can increase sensitivity for early HCC detection compared with ultrasound, their routine use is limited by physical harms (e.g., radiation and contrast exposure) and high costs.[4,6] Studies evaluating alternative, cheaper MRI-based surveillance strategies, including abbreviated and noncontrast protocols, are ongoing.[7] However, until safer and more cost-effective options are available, ultrasound remains the preferred imaging modality for HCC surveillance.

Serum tumor markers are another attractive option to improve sensitivity for early tumor detection. Although AFP, the best studied serological test, has insufficient sensitivity and specificity for early tumor detection if used alone, it appears to be of significant benefit when used in combination with ultrasound. The meta-analysis of cohort studies comparing ultrasound with or without AFP reported the pooled sensitivity of ultrasound alone for early-stage HCC is significantly lower than when using ultrasound with AFP (45% versus 63%; relative risk [RR] 0.81, 95% CI: 0.71-0.93).[4] (Fig. 1) Although ultrasound alone has higher specificity than ultrasound with AFP (92% versus 84%; RR 1.08, 95% CI: 1.05-1.09),[4] the clinical significance of this difference is unclear. A single-center study characterizing surveillance-related harms reported a higher proportion of patients experienced ultrasound-related physical harms than AFP-related harms (22.8% versus 11.4%; $P < 0.001$), likely because of providers monitoring low-level false-positive AFP levels instead of performing diagnostic evaluation in all cases.[6] Additional strategies such as AFP-adjusted algorithms, tailoring cutoffs to liver disease causative factors, and using longitudinal measurements have been shown to improve AFP accuracy and further mitigate AFP-related surveillance harms.[8-10] The benefit of AFP for HCC surveillance may also increase over

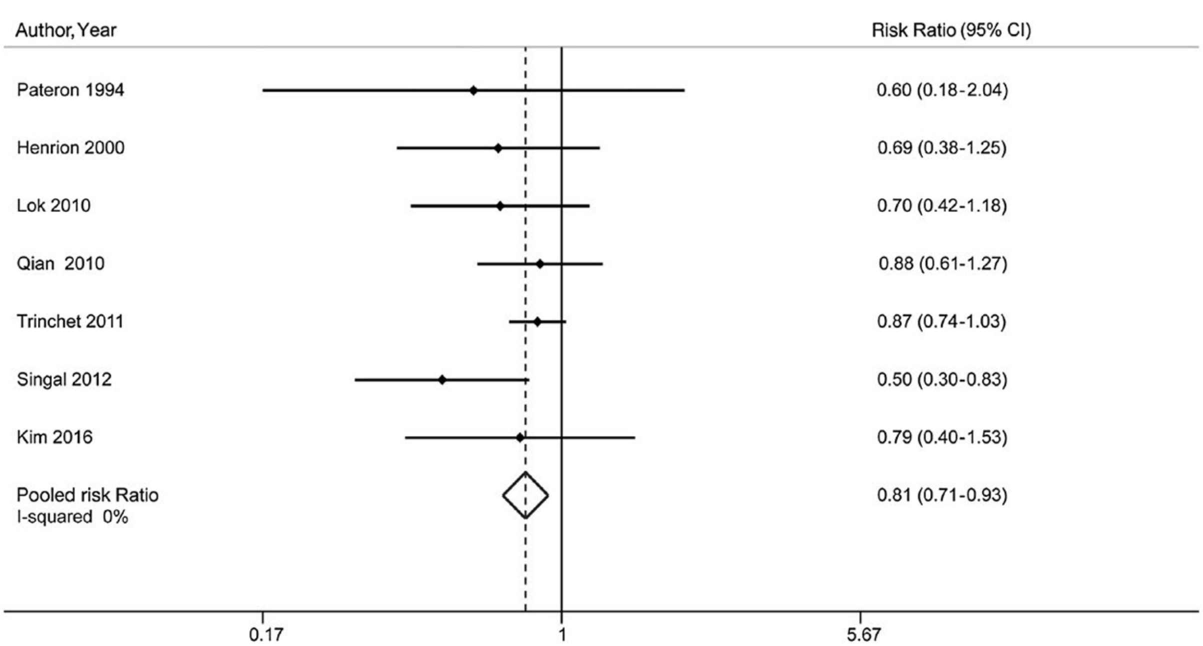

FIG 1 Ultrasound alone has lower sensitivity compared with ultrasound with AFP for early HCC detection.[3]

Arterial phase hyperenhancement (APHE)		No APHE		APHE (not rim)		
Observation size (mm)		<20	≥20	<10	10-19	≥20
Count major features: • "Washout" (not peripheral) • Enhancing "capsule" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5: Observations in this cell are categorized LR-4, except:
- LR-5g, if ≥ 50% diameter increase in < 6 months (equivalent to OPTN 5A-g)
- LR-5us, if "washout" and visibility at screening ultrasound (per AASLD HCC criteria)

FIG 2 LI-RADS (version 2017) classification of liver nodules.[14]

time as HCC epidemiology shifts from viral-related to alcohol and nonalcohol steatohepatitis, with resultant improvement in AFP specificity.

Several additional biomarkers are undergoing evaluation, including AFP-L3, des-γ-carboxyprothrombin (DCP), osteopontin, glycosylated proteins, and circulating tumor cells.[11] Given heterogeneity within and between HCC lesions, it is possible, if not likely, that a single biomarker will not be sufficient and a panel incorporating multiple biomarkers will be needed. One such panel is the GALAD score, which includes gender, age, and three biomarkers (AFP, AFP-L3, and DCP).[12] This panel has been evaluated in multicenter case-control studies with a sensitivity for early-stage HCC ranging from 60% to 80% and acceptable specificity of approximately 90%.[12,13] Several of these novel biomarkers have promising results in phase 2 (case-control) biomarker studies but still require validation in phase 3 (cohort) biomarker studies.[11] There are ongoing multicenter efforts, such as the National Cancer Institute–funded Hepatocellular carcinoma Early Detection Study, to validate these biomarkers. While awaiting these data, the combination of ultrasound and AFP appears to be the optimal strategy to maximize HCC surveillance value.

HCC RECALL AND DIAGNOSIS

Patients with a lesion ≥1 cm on ultrasound or AFP >20 ng/mL on surveillance imaging should undergo diagnostic evaluation with a multiphasic CT or MRI.[14] The AASLD guidelines endorse the use of LI-RADS, a comprehensive system that aims to standardize the interpretation and reporting for diagnostic imaging. LI-RADS categorizes liver nodules based on likelihood of HCC ranging from definitely benign (LR-1) to intermediate probability (LR-3) to definite HCC (LR-5).[15] The likelihood of HCC is determined by a combination of major and minor criteria, including arterial enhancement, delayed washout, enhancing capsule, and threshold growth (Fig. 2).

In patients with cirrhosis, a diagnosis of HCC can be made radiographically, without histological confirmation, if typical imaging characteristics are present.[2] Therefore, patients with LR-5 lesions can undergo HCC treatment without a need for histological confirmation. Of note, lesions with a characteristic appearance but occurring in low-risk patients such as those without cirrhosis cannot be classified as LR-5 and would still require biopsy for diagnosis. Indeterminate lesions, that is, LR-3 or LR-4 lesions, can pose a diagnostic challenge because some are atypical-appearing HCCs and others are benign lesions. Prior AASLD guidelines recommended biopsy of all indeterminate lesions[14]; however, the most recent guidelines discourage routine biopsy of indeterminate nodules given biopsy-related harms, its low sensitivity in smaller lesions, and the low likelihood of malignancy in some indeterminate nodules.[2,16] The most recent guidelines now recommend a choice of biopsy, close interval repeat imaging, or using an alternative diagnostic modality (CT versus MRI) based on the pretest probability of HCC and patient preference.

Biomarkers currently have no role in the diagnostic algorithm for HCC. Although AFP was previously included in the diagnostic algorithm, it is no longer recommended given insufficient sensitivity and specificity.

CONCLUSION

Updated AASLD guidelines have notable changes, including the reinstatement of AFP for HCC surveillance and the incorporation of LI-RADS for diagnosis. Recent studies have demonstrated that using ultrasound with AFP has superior sensitivity for early tumor detection than ultrasound alone. While awaiting further evaluation of novel imaging and biomarkers, ultrasound and AFP should be considered as the standard surveillance strategy in patients with cirrhosis. Patients with positive surveillance tests should be referred for diagnostic evaluation with four-phase CT or MRI. LI-RADS offers a standard nomenclature for classifying liver lesions, including definite HCC, in at-risk patients.

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